PATENT

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Title	**SELECTIVE ENZYME TREATMENT OF SKIN CONDITIONS**
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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF HOWARD FEIN, M.D.
PURSUANT TO 37 C.F.R. §1.132

I, HOWARD FEIN M.D., declare as follows:

1. I am the named inventor in the above-identified patent application.

2. I hold a Doctor of Medicine from the University of Southern California School of Medicine. I have over seven years of experience in dermatology and treatment of skin conditions, which is the subject of the application. I have read the Office Action of September 28, 2006 and understand the Examiner's position.

3. My method selectively removes a seborrheic keratosis condition from skin using trypsin. A formulation containing trypsin as the sole active agent is applied to skin at the site of the seborrheic keratosis. One or more applications are used within at least 18 minutes. Multiple applications may also be used, such as one or two applications a day, or one to ten applications a day. Because none of Klein, Fortney, or SU Patent 1685448, alone or combined with Zaias, Rawlings, or Burbach, teach or suggest or motivate a method using trypsin to treat seborrheic keratosis, and in which the parameters (time, concentration, etc.) for applying the enzyme is selected for the patient's particular situation, I disagree with the Examiner that each of these references renders my invention obvious.

4. As I understand the Examiner requested during the January 9, 2007 personal interview with my patent attorney, I provide a description of seborrheic keratosis, as known to one skilled in the art and supported

at least in "Histopathology of the Skin", Lever and Schaumburg-Lever, 1983, pp. 476-482 (J.B. Lippincott Company, Philadelphia, PA), a copy of which is attached.

5. Seborrheic keratosis is a pathological skin tumor, referred to as a neoplasm (as recognized by one skilled in the art, pathology does not imply malignancy). The new growth is a lesion that is sharply demarcated, brownish in color, and slightly raised. The lesion may have a smooth or verrucous surface, but it characteristically shows keratotic plugs. The size of the lesion ranges in size from a few millimeters to several centimeters in diameter.

6. There are six general types of seborrheic keratoses. These are acanthotic, hyperkeratotic, reticulated, clonal, irritated, and melanoacanthoma. A single lesion may contain one type, or may contain more than one type. All types, however, have hyperkeratosis, acanthosis, and papillomatosis. Acanthosis is due entirely to the upward extension of the tumor, manifest as a raised lesion on a skin surface. The acanthotic type is the most common of seborrheic keratosis.

7. There are two types of cells in the acanthotic epidermis. The first cell type has the appearance of squamous cells that are normally found in the epidermis. The second cell type has the appearance of basaloid cells that resemble basal cells found in the basal layer of the epidermis; upon histologic examination, areas of edema and intercellular bridges can be seen. Thus, the seborrheic keratosis lesion has a cellular layer resembling the epidermis.

8. As described in the Lever and Schaumburg-Lever reference, all six types of seborrhic keratoses affect the epidermal layer of the skin.

9. One embodiment of my method treating seborrheic keratosis is described in Example 1, page 22, of my application. A composition consisting of 2.5% trypsin is applied to a lesion (as shown in my Fig. 1) six times at intervals of three minutes. The timing and number of intervals can be varied according to the size of the lesion. Erosion was present at the treatment site following the protocol (Fig. 2). The treated area was washed and dressed. No other treatment was applied. At three weeks the lesion was eliminated without scarring (Fig. 3). At six months the treated area appeared the same as the surrounding unaffected skin areas (Fig. 4).

10. The SU Patent 1685448 discloses a treatment protocol of applying, for up to two days, an ointment containing trypsin and other components. There is no indication of how many times the ointment was applied during this time. The ointment also contained dimethylsulfoxide (DMSO) at a concentration that effects enzyme activity. I described this in my August 15, 2005 Declaration.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the subject application or any patent issued thereon.

1/24/07

Date

Howard Fein, M.D.

(see p. 378) (Kuhlwein et al) and of leukoedema of the oral mucosa (see below).

Leukoedema of the Oral Mucosa

Leukoedema of the oral mucosa is a common condition that, when pronounced, shows a clinical and histologic resemblance to oral white sponge nevus. However, leukoedema differs from white sponge nevus by being patchy rather than diffuse, by having exacerbations and remissions and adult onset, and by not being inherited (Duncan and Su).

Histopathology. In leukoedema of the oral mucosa, as in oral white sponge nevus, the suprabasal epithelial cells show marked intracellular edema. The nuclei appear smaller than normal.

Lingua Geographica

In geographic tongue, also referred to as superficial migratory glossitis, the dorsum of the tongue shows irregularly shaped red patches surrounded by a whitish, raised border a few millimeters wide. The patches change configuration from day to day.

Histopathology. Whereas the dorsum of the tongue normally shows a granular and a horny layer (see p. 11), these layers are absent in the red patches of lingua geographica. Along the whitish border, the epithelium shows irregular thickening and infiltration of neutrophils. In its upper portion, the epithelium shows collections of neutrophils within the interstices of a spongelike network formed by degenerated and thinned epithelial cells (Dawson; Marks and Radden). The histologic picture thus shows Kogoj's spongiform pustules, which are indistinguishable from those seen in pustular psoriasis.

Histogenesis. The presence of spongiform pustules generally is regarded as diagnostic of pustular psoriasis and as almost specific for it (see p. 145), even though it rarely occurs in other pustules, such as those caused by *Candida albicans* (Degos et al). It has therefore been suggested that geographic tongue represents a localized form of pustular psoriasis (O'Keefe et al). However, even though pustular psoriasis and lingua geographica may both show annular lesions on the tongue, pustular psoriasis of the mouth generally shows clinical evidence of pustules and is usually seen also in other areas of the mouth. It is therefore best to regard lingua geographica as a separate entity.

SEBORRHEIC KERATOSIS

Seborrheic keratoses are very common lesions. There may be only one lesion, but there are often many. They occur mainly on the trunk and face but also on the extremities, with the exception of the palms and soles. Seborrheic keratoses usually do not appear before middle age. They are sharply demarcated, brownish in color, and slightly raised, so that they often look as if they are stuck on the surface of the skin. Most of them have a verrucous surface, which has a soft, friable consistency. Some, however, have a smooth surface but characteristically show keratotic plugs. Although most lesions measure only a few millimeters in diameter, a lesion may occasionally reach a size of several centimeters. Crusting and an inflammatory base are found if the lesion has been subjected to trauma. Occasionally, seborrheic keratoses are pedunculated, especially on the neck and upper chest, and then clinically resemble soft fibromas (see p. 600).

Histopathology. Seborrheic keratoses show a considerable variety of histologic appearances. Six types are generally recognized: acanthotic, hyperkeratotic, reticulated, clonal, irritated, and melanoacanthoma. Often, more than one type is found in the same lesion. In addition, two clinical variants of seborrheic keratosis will be described. They are dermatosis papulosa nigra and stucco keratosis.

All types of seborrheic keratosis have in common hyperkeratosis, acanthosis, and papillomatosis. The acanthosis in most instances is due entirely to upward extension of the tumor. Thus, the lower border of the tumor is even and lies on a straight line that may be drawn from the normal epidermis at one end of the tumor to the normal epidermis at the other end (Fig. 26-2). Two types of cells are usually seen in the acanthotic epidermis: squamous cells and basaloid cells. The former have the appearance of squamous cells normally found in the epidermis, whereas the basaloid cells are small and uniform in appearance and have a relatively large nucleus. In areas of slight intercellular edema, intercellular bridges can be easily recognized (Andrade and Steigleder). Thus, they resemble the basal cells found normally in the basal layer of the epidermis.

Acanthotic Type. In the acanthotic type, the most common type of seborrheic keratosis, hyperkeratosis and papillomatosis often are slight, but the epidermis is greatly thickened. Although only narrow papillae are included in the thickened epidermis in some cases, one can see in other lesions a retiform pattern composed of thick, interwoven tracts of epithelial cells surrounding

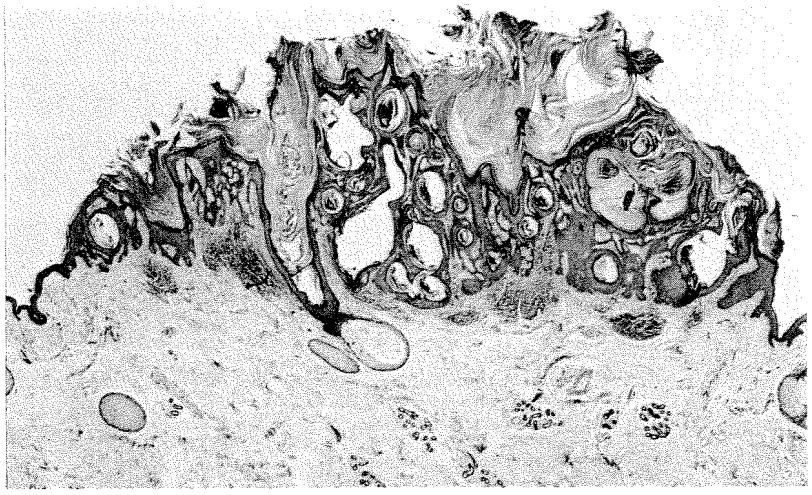

Fig. 26-2. Seborrheic keratosis, acanthotic type
Low magnification. The lower border of the tumor in general follows a straight line from the normal epidermis at one end of the tumor to the normal epidermis at the other end. (×25)

islands of connective tissue (Fig. 26-3). Horny invaginations that on cross sections appear as pseudo-horn cysts are numerous. In addition, there also are true horn cysts, which, like the pseudo-horn cysts, show sudden and complete keratinization. The true horn cysts begin as foci of orthokeratosis within the substance of the lesion (Sanderson). In time, they enlarge and are carried by the current of epidermal cells toward the surface of the lesion, where they unite with the invaginations of surface keratin. In the greatly thickened epidermis, basaloid cells usually outnumber squamous cells.

The amount of melanin in seborrheic keratoses of the acanthotic type is often greater than normal. Excess amounts of melanin are seen in about one third of the specimens stained with hematoxylin–eosin (Becker); staining with silver reveals excess amounts in about two thirds of the cases (Lennox). In dopa-stained sections, melanocytes are limited to the dermal-epidermal junctional layer present at the base of the tumor and at the interfaces between the tumor tracts and the islands of dermal stroma (Mevorah and Mishima). The melanin, largely present in keratinocytes, is in most instances also limited to keratinocytes located at the dermal-epidermal junction. Only deeply pigmented lesions show melanin widely distributed throughout the tumor within basaloid cells (Mishima and Pinkus).

A mononuclear inflammatory infiltrate is seen quite frequently in the dermis underlying a seborrheic keratosis. The inflammation may impinge on the tumor in a lichenoid or eczematous pattern. In the lichenoid pattern, a bandlike infiltrate is seen

Fig. 26-3. Seborrheic keratosis, acanthotic type
High magnification. Thick, interwoven tracts of epidermal cells compose the tumor. Most of the epidermal cells have the appearance of epidermal basal cells and are referred to as basaloid cells. Interspersed are cystic inclusions of horny material representing either horn cysts, when they form within the tumor, or pseudo-horn cysts, when they consist of horny invaginations. (×100)

hugging the basal cell layer of the tumor. In the eczematous pattern, there is exocytosis leading to spongiosis. Squamous eddies, typical of irritated seborrheic keratoses, are only rarely seen in inflamed seborrheic keratoses (Berman and Winkelmann).

Formation of an in situ carcinoma within an acanthotic seborrheic keratosis, so-called bowenoid transformation, is seen occasionally (Rahbari; Baer et al). It seems to occur predominantly in lesions located in sun-exposed areas of the skin, so that sun damage may be a factor (Booth). In one reported case, a metastasis in a regional lymph node was found (Christeler and Delacrétaz). On rare occasions, a basal cell epithelioma may form within an acanthotic seborrheic keratosis and may extend from there into the underlying dermis (Balabanow and Angelow; Mikhail and Mehregan).

Histogenesis. *Electron microscopic examination* has confirmed the light microscopic impression that the small basaloid cells seen in the acanthotic type of seborrheic keratosis are related to cells of the epidermal basal cell layer rather than to the basalioma cells of basal cell epithelioma. They possess a fair number of desmosomes and a moderate number of tonofilaments that differ from those present in cells of the epidermal basal cell layer only by showing less orientation (Braun-Falco et al).

Hyperkeratotic Type. In the hyperkeratotic type, also referred to as the digitate or serrated type, hyperkeratosis and papillomatosis are pronounced, whereas acanthosis is not very conspicuous. The numerous digitate upward extensions of epidermis-lined papillae often resemble church spires. The histologic picture then resembles that seen in acrokeratosis verruciformis of Hopf (see p. 74). The epidermis consists largely of squamous cells, although small aggregates of basaloid cells may be seen here and there. As a rule, no excess amounts of melanin are found.

Reticulated Type. In the reticulated or adenoid type of seborrheic keratosis, numerous thin tracts of epidermal cells extend from the epidermis and show branching and interweaving in the dermis. Many tracts are composed of only a double row of basaloid cells (Fig. 26-4). Horn cysts and pseudo-horn cysts are absent in purely reticulated lesions; however, the reticulated type often also shows areas of the acanthotic type, and horn cysts and pseudo-horn cysts are commonly seen in these areas. The basaloid cells of the reticulated type of seborrheic keratosis usually show marked hyperpigmentation.

There is both clinical and histologic evidence of a close relationship between lentigo senilis and the reticulated type of seborrheic keratosis. A lesion of lentigo senilis may even become a reticulated seborrheic keratosis through exaggeration of the process of downward budding of pigmented basaloid cells (see p. 697) (Mehregan, 1975).

Clonal Type. In the clonal, or nesting, type of seborrheic keratosis, well-defined nests of cells are located within the epidermis. In some instances, the nests resemble foci of basal cell epithelioma, since the nuclei appear small and dark-staining and intercellular bridges are seen in only a few areas (Fig. 26-5). The histologic picture in such cases has been erroneously interpreted by some authors as representing an intraepidermal epithelioma of Borst–Jadassohn (see p. 571) (Mehregan and Pinkus). In other instances of clonal seborrheic keratosis, the nests are composed of fairly large cells showing distinct intercellular bridges (Fig. 26-6).

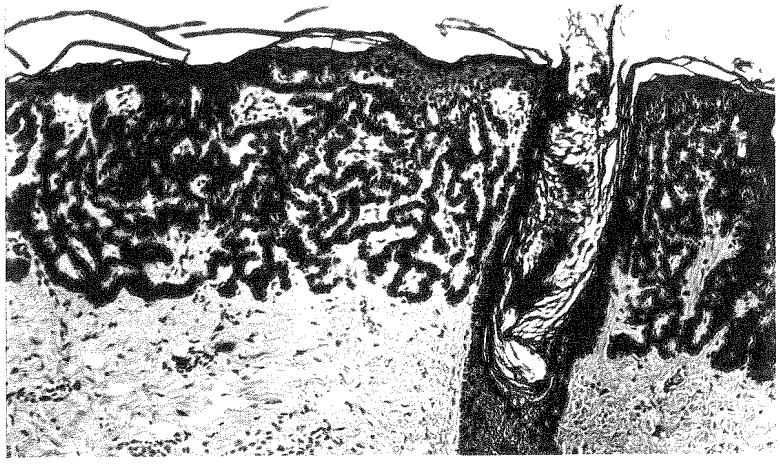

Fig. 26-4. Seborrheic keratosis, adenoid type
Thin, interwoven tracts composed of a double row of epidermal basal cells compose the tumor. No cystic inclusions of horny material are present. (×100)

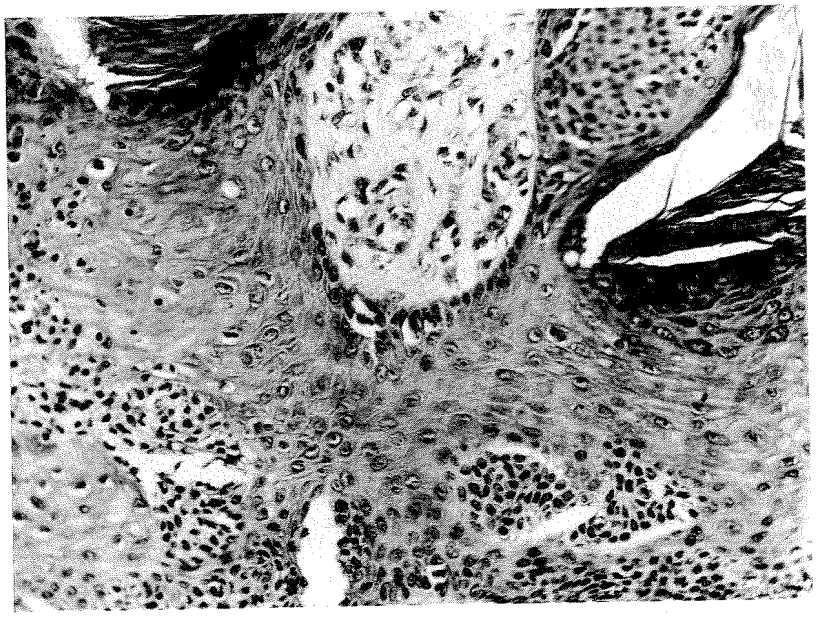

Fig. 26-5. Seborrheic keratosis, clonal type
Well-defined nests of small basaloid cells are present. The nests resemble foci of basal cell epithelioma, but intercellular bridges can be recognized in some areas. (×200)

Fig. 26-6. Seborrheic keratosis, clonal type
Well-defined nests of large cells with distinct intercellular bridges are present. (×200)

Irritated Type. In the irritated, or activated, type of seborrheic keratosis, the characteristic feature is the presence of numerous whorls or eddies composed of eosinophilic flattened squamous cells arranged in an onion-peel fashion, thus resembling poorly differentiated horn pearls (Fig. 26-7). These "squamous eddies," however, are easily differentiated from the horn pearls of squamous cell carcinoma by their large number, small size, and circumscribed configuration. Irritated seborrheic keratoses, in addition, may show areas of downward proliferation breaking through the horizontal demarcation generally present in nonirritated seborrheic keratoses (Sim-Davis et al; Indianer). Frequently, some of these proliferations are seen to originate from the walls of keratin-filled invaginations. Inflammation beneath irritated seborrheic keratoses usually is mild or absent, indicating that irritated seborrheic keratoses are different from inflamed seborrheic keratoses (see p. 477).

Fig. 26-7. Irritated seborrheic keratosis
Numerous whorls of eosinophilic flattened squamous cells, so-called squamous eddies, are present. They differ from the horn pearls of squamous cell carcinoma by their large number, small size, and circumscribed configuration. (×200)

Histogenesis. Formation of numerous squamous eddies is the result of the "activation" of resting basaloid cells into squamous cells. This unique and highly diagnostic feature of irritated or activated seborrheic keratoses, as well as their downward proliferation, is the result of irritation. This has been proved experimentally by the excision of seborrheic keratoses either after a previous biopsy (Morales and Hu) or after irritation with croton oil (Mevorah and Mishima).

The identical histologic picture as seen in irritated seborrheic keratosis has been described under designations such as inverted follicular keratosis (Helwig; Mehregan, 1964) and follicular poroma (Duperrat and Mascaro; Grosshans and Hanau). As these terms indicate, the authors regard the keratin-filled invaginations as follicular infundibula and the proliferations arising from them as composed of cells of the follicular infundibulum. Aside from the fact that the follicular infundibulum consists of cells with the same type of keratinization as the surface epidermis, there is evidence that seborrheic keratoses may incorporate the cells of the infundibular portion of the hair follicle and even are partially derived from these cells. Some seborrheic keratoses even contain aggregates of vellus hairs within the keratinous invaginations, an occurrence analogous to trichostasis spinulosa (see p. 202) (Kossard et al). Thus, whereas some authors merely concede that irritated seborrheic keratoses and inverted follicular keratoses may be histologically indistinguishable (Headington; Brownstein and Shapiro), others regard the two disorders as identical (Sim-Davis et al; Indianer; Kossard et al). Because of their histologic similarity and, particularly, because of the highly specific appearance of the squamous eddies that occur exclusively in these two conditions, they are best regarded as identical.

Melanoacanthoma. In one rather rare histologic variant of seborrheic keratosis referred to as melanoacanthoma (Mishima and Pinkus), one finds numerous large, pigment-filled melanocytes distributed throughout the lesion. In some instances, they are apparent even in sections stained with hematoxylin-eosin (Mishima and Pinkus; Schlappner et al). In any case, staining with silver reveals numerous melanocytes possessing large dendrites and containing considerable amounts of melanin, whereas the keratinocytes contain hardly any melanin (Delacrétaz; Matsuoka et al). Thus, melanoacanthoma differs from the common pigmented seborrheic keratosis, in which there are only few melanocytes and the melanin is found almost entirely within the keratinocytes.

Histogenesis. It is obvious that at least a partial block in the transfer of melanin from melanocytes to keratinocytes exists in melanoacanthoma. Since some melanoacanthomas have the histologic appearance of an irritated seborrheic keratosis, it has been assumed that the transfer of melanin to keratinocytes is blocked as a result of the transformation of most basaloid cells into squamous cells. However, in a study in which seborrheic keratoses were changed into irritated seborrheic keratoses by croton oil or surgical trauma, no changes characteristic of melanoacanthoma were seen (Mevorah and Mishima). Thus, it appears likely that melanoacanthoma is a benign mixed tumor of melanocytes and keratinocytes, as first described (Mishima and Pinkus).

Leser–Trélat Sign

The Leser–Trélat sign is characterized by the sudden appearance of numerous seborrheic keratoses in association with a malignant tumor. Although several reports have appeared in recent years concerning this sign, the association may well be purely coincidental, and the validity of the sign is therefore not generally accepted (Gitlin and Pirozzi; Lambert et al). In the opinion of some, the Leser–Trélat sign applies only to cases in

which the seborrheic keratoses are pruritic and the skin was previously free of them (Ronchese).

Although the malignant tumor in most of the reported cases consisted of an abdominal adenocarcinoma (Liddell et al), the associated malignant disease in some reports was leukemia (Kechijian et al) or mycosis fungoides (Lambert et al).

Histopathology. The histologic appearance of the seborrheic keratoses in the Leser–Trélat sign does not differ from that of other seborrheic keratoses (Schwartz and Burgess). Nevertheless, they have been interpreted as "an incomplete form of acanthosis nigricans" (Sneddon and Roberts) or as "potentially representing an early stage of acanthosis nigricans" (Ronchese). There are indeed cases in which the seborrheic keratoses seen in this sign were either accompanied (Schwartz and Burgess) or followed by acanthosis nigricans (Ronchese) (see p. 430).

Dermatosis Papulosa Nigra

Dermatosis papulosa nigra is found in about 35% of all adult blacks, and often has its onset during adolescence (Hairston et al). The lesions are located predominantly on the face, especially in the malar regions, but may also occur on the neck and upper trunk. They usually consist of small, smooth, pigmented papules, except on the neck and trunk, where some of them may be pedunculated.

Histopathology. The lesions have the histologic appearance of seborrheic keratoses but are smaller in size. Most lesions are of the acanthotic type and show thick interwoven tracts of epithelial cells. The cells are largely squamous in appearance, with only a few basaloid cells (Hairston et al). Horn cysts are quite common. An occasional lesion shows a reticulated pattern, in which the tracts are composed of a double row of basaloid cells. Melanin pigmentation is pronounced in all lesions.

Stucco Keratosis

Stucco keratoses are small, grayish white seborrheic keratoses 1 mm to 3 mm in diameter located in symmetric arrangement on the distal portions of the extremities, especially the ankles. They can easily be scraped off without any resultant bleeding.

Histopathology. Stucco keratoses have the appearance of the hyperkeratotic type of seborrheic keratosis, showing the church-spire pattern of upward-extending papillae (Willoughby and Soter; Braun-Falco and Weissmann). Horn cysts and basaloid cells are usually absent (Kocsard and Carter).

CLEAR CELL ACANTHOMA

Clear cell acanthoma, a tumor that is clinically and histologically quite distinct, was first described in 1962 (Degos et al). It is not rare, so that, by 1977, more than 200 cases had already been reported (Kerl).

In most instances, the lesion is solitary and is located on the legs. Usually, it consists of a slowly growing, sharply delineated, red nodule or plaque 1 cm to 2 cm in diameter. In most cases, it is covered with a thin crust and exudes some moisture. A collarette is often seen at the periphery. It has been said that the lesion appears stuck on, like a seborrheic keratosis, and is vascular, like a granuloma pyogenicum (Fine and Chernosky).

Histopathology. Within a sharply demarcated area of the epidermis, all epidermal cells, with the exception of cells of the basal cell layer, appear strikingly clear and slightly enlarged (Fig. 26-8). The nuclei of the clear epidermal cells appear normal. When staining is carried out with the periodic acid-Schiff (PAS) reaction, the presence of large amounts of glycogen is revealed within the cells (Degos et al; Wells and Wilson Jones).

Slight spongiosis is present between the clear cells. The rete ridges are elongated and may show intertwining (Kerl). The surface shows parakeratosis with few or no granular cells. The acrosyringia and acrotrichia within the tumor retain their normal stainability (Zak and Girerd). There is an absence of melanin within the tumor cells, but sparsely scattered, weakly dopa-positive melanocytes are present, and melanin can be seen within the melanocytes and their dendritic processes on silver staining (Wells and Wilson Jones).

A conspicuous feature in most lesions is the presence throughout the epidermis of numerous neutrophils, many of which show fragmentation of their nuclei (Fig. 26-9). The neutrophils often form microabscesses in the parakeratotic horny layer (Wilson Jones and Wells; Trau et al). Dilated capillaries are seen in the elongated papillae and often also in the dermis underlying the tumor (Wells and Wilson Jones). In addition, a mild to moderately severe cellular infiltrate composed largely of lymphoid cells is present in the dermis.

Beneath the tumor, some cases have shown hyperplasia of sweat ducts (Wilson Jones and Wells) or syringomalike proliferations (Cramer).

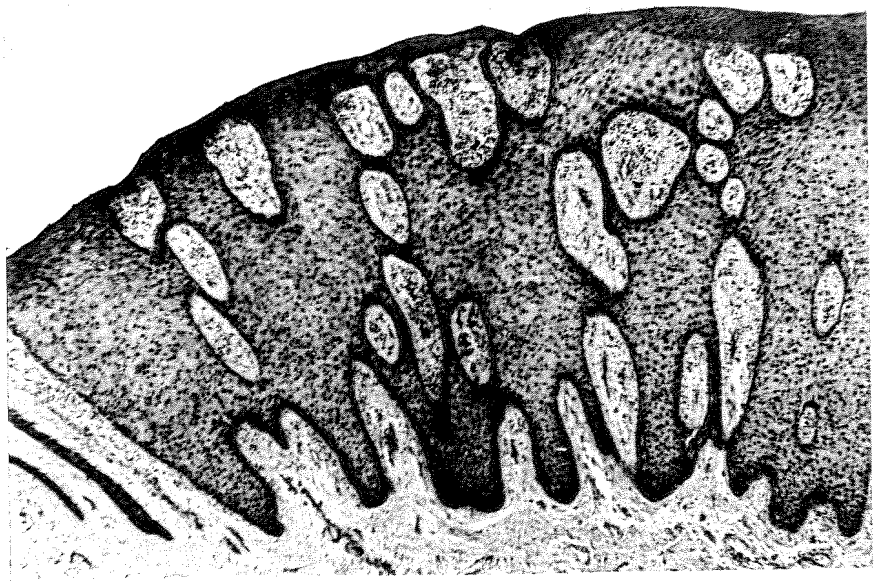

Fig. 26-8. Clear cell acanthoma
Low magnification. The cells within the thickened epidermis appear strikingly clear because of the presence of large amounts of glycogen. (×100)

Fig. 26-9. Clear cell acanthoma
High magnification. Neutrophils and nuclear dust are scattered through the tumor. At the lower border, part of an acrosyringium is visible with cells that have retained their normal stainability. (×400)

Histogenesis. On *histochemical examination,* phosphorylase is absent in clear cell acanthoma except for the basal cell layer. This enzyme normally is present in the epidermis and is necessary for the degradation of glycogen (Desmons et al).

Electron microscopy reveals glycogen granules in the tumor cells, except in the cells of the basal cell layer. In the lower portion of the tumor, the glycogen granules are seen largely around the nuclei. In the upper portion, however, the amount of glycogen is increased, and the granules are seen to infiltrate between the tonofilaments (Desmons et al).

Although the melanocytes, including their dendrites, contain melanosomes, hardly any melanosomes are present within the tumor cells, indicating a blockage in the transfer of melanosomes from the melanocytes to the tumor cells (Hu and Sisson).

EPIDERMAL CYST

Epidermal cysts are slowly growing, elevated, round, firm, intradermal or subcutaneous tumors that cease growing after having reached a size of 1 cm to 5 cm in diameter. They occur most commonly on the face, scalp, neck, and trunk. Although epidermal cysts in most instances arise spontaneously, they occasionally form as a result of the traumatic implantation of epidermis into the dermis or subcutis (Onuigbo; Leonforte). Usually, a patient has only one or a few epidermal cysts, rarely many. In Gardner's syndrome, however, numerous epidermal cysts occur, especially on the scalp and face (see p. 607).

Histopathology. Epidermal cysts have a wall composed of true epidermis, as seen on the skin

Histopathology of the Skin

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6th Edition

6

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